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ENHANCEMENT OF SOLUBILITY & DISSOLUTION RATE OF NIFEDIPINE BY USING NOVEL SOLUBILIZER SEPITRAP 80 & SEPITRAP 4000

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ABSTRACT

The enhancement in solubility and dissolution rate of BCS class-II drug Nifedipine was achieved by simple physical mixture with sepitrap 80 & sepitrap 4000 in 1:1 & 1:2 proportion. The saturation solubility studies shows 263 % & 368 % increase in the solubility in physical mixture of Nifedipine with sepitrap 80 & sepitrap 4000 respectively. The physicochemical properties of pure Nifedipine compared to their physical mixtures with sepitrap 80 & sepitrap 4000 were determined using FTIR, DSC & PXRD. The FTIR and DSC studies shows no any interaction in Nifedipine and sepitrap, the marked broadening and distinct reduction in intensity with shifting of drug endotherm was displayed physical mixture with sepitrap demonstrate positive effect. The PXRD diffractograms shows distinctive peaks but reduction in peak intensity in terms of counts indicating conversion of drug in amorphous forms. The surface morphology of the prepared physical mixture was examined by SEM which indicating no significant change in its surface morphology due to no use any solvent during the preparation of physical mixture . Photostability studies shows that rate of photo degradation is very slow in Physical mixture with sepitrap as compared to pure Nifedipine. Dissolution studies in SGF & SIF shows that significant enhancement by use of novel solubilizer sepitrap 80 as well as sepitrap 4000 in 1:2 proportions. The physical mixture containing sepitrap 4000 was found stable as there was no any significant change in appearance and drug dissolution after three month stability studies.

Keywords: Nifedipine, sepitrap 80, sepitrap 4000, physical mixture, solubility enhancement.

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1. INTRODUCTION

Nifedipine is an oral calcium-channel blocking agent, widely used in the treatment of angina pectoris and hypertension. Nifedipine is a poorly water-soluble drug and its oral bioavailability is very low. Diseases like angina, asthma, epilepsy etc. require immediate drug response to manage the disease condition. Improvement of the aqueous solubility of poorly water-soluble drugs is one of the important factors for the enhancement of absorption and obtaining adequate oral bioavailability [1].

The various methods reported till the date for dissolution rate enhancement of Nifedipine (model drug) include compaction with hydroxypropylmethylcellulose [2], co-grinding with HPMC [3] or bile salts [4], formation of solid dispersions as co-precipitates or co-evaporates with mannitol[5], phosphatidylcholine esters [6], HPMC [7], Chitosan derivatives [8], polyethylene glycols [9] and polyoxyethylene–polyoxypropylene copolymers [10], and inclusion complexes with beta-cyclodextrin [11].

In addition to the common solubility enhancement techniques which was reported by various researchers the use of novel solubilizer is one of the challenging approach for enhancement of solubility of poorly soluble drug like Nifedipine. The use of novel solubilizer like SEPITRAP 80 & SEPITRAP 4000 got an attention because simplicity of process that is no need to go for any complex procedure which may need to perform in above mentions methods. Only simple physical mixture of API with SEPITRAP 80 & SEPITRAP 4000 in various proportions is most prominent for enhancement of solubility and dissolution rate of poorly soluble drug like Nifedipine from solid oral formulations [12]. The exposure of some drugs to light leads to photodecomposition. These drugs undergo important chemical changes, accompanied by alternation in their activities and in some cases total loss of their therapeutic activity [13]. Nifedipine is very highly sensitive to photo oxidation & photodegradated products have no pharmacological activity [14,15] hence there is necessary to protect during formulation and need to evaluate for its Photostability.

2. MATERIAL & METHODS

2.1 Material:

Nifedipine was obtained as a gift sample from Zydus Cadila ltd, Ahmadabad, India. Sepitrap 4000, Sepitrap 80 were gifted by Seppic, Mumbai. All other chemicals and solvents used were of pharmaceutical and analytical grade. Double distilled water was used throughout the study for all the experimental procedures.

2.2 Preparation of Nifedipine & Sepitrap Physical mixture:

The 100 mg of Nifedipine weighed accurately & physical mixtures of Nifedipine with Sepitrap 80 & Sepitrap 4000 was prepared by simple spatulation method in the various proportions like 1:1 & 1:2. [16 -18]. Various proportion used for physical mixtures was depicted in table no.1

Table 1: Physical mixtures of Nifedipine with Sepitrap 80 & Sepitrap 4000

Batch No	Drug (mg)	SEPITRAP 80 (mg)	SEPITRAP 4000 (mg)
PM1	100	100 (1:1 ratio)	---
PM2	100	200 (1:2 ratio)	---
PM3	100	---	100 (1:1 ratio)
PM4	100	---	200 (1:2 ratio)

2.3 Characterization of Nifedipine & Sepitrap Physical Mixtures:

2.3.1 Saturation solubility studies

A saturation solubility study was carried out to determine increase in the solubility of pure Nifedipine [19] compared with the Physical mixtures of Nifedipine with Sepitrap 80 & sepitrap 4000. Excess amount of the drug& Physical mixtures of Nifedipine with Sepitrap 80 & sepitrap 4000 were added to the 250 mL conical flasks containing 25 mL of double distilled water. Then flasks were covered with cellophane membrane to avoid any loss of solvent and then kept in rotary shaker for 48 h at 37± 0.5^{0}C. The extra care was taken by covering the flask with black paper to protect the drug from photo degradation studies by considering photosensitive nature of Nifedipine. Aliquots were then withdrawn and filter through Whatman filter paper. The concentration of Nifedipine was determined by using UV visible spectrophotometer at 238nm (Shimadzu UV spectrophotometer 1800) after appropriate dilution [20.] Three determinations were carried out for each sample to calculate the solubility of Nifedipine. The solubility of Nifedipine and percent increase in solubility due to use of sepitrap 80 & sepitrap4000 are depicted in figure no.1

2.3.2 Fourier Transform Infrared spectrophotometer studies:

FT-IR has been employed as a useful tool to identify drug excipient interaction. Samples were analyzed by the potassium bromide pellet method in an IR spectrophotometer (Alpha T Bruker) in the region from 4000 to 400 cm^{-1}. Physical mixtures of drug with sepitrap 80 & sepitrap 4000 were evaluated by comparing FT-IR spectra of physical mixtures to that of pure drug spectra. The FT-IR spectra of Pure Nifedipine, Physical mixture of Nifedipine- Sepitrap 80 & Physical mixture of Nifedipine- Sepitrap 4000 are shown in figure No.2

2.3.4 Differential scanning calorimeter (DSC) Analysis:

Differential scanning calorimetry (DSC) has been one of the most widely used calorimetric techniques to study the solid state interaction of drug with Physical mixtures [21]. Samples of the pure drug & physical mixture of drug sepitrap were taken in flat-bottomed aluminum pans and heated over a temperature range of 30 to 300 °C at a constant rate of 10°/min with purging of nitrogen (50 ml/min) using alumina as a reference standard in a differential scanning calorimeter (Mettler Toledo, Staresw 920). The DSC thermogram of Pure Nifedipine, Physical mixture of Nifedipine- Sepitrap 80 & Physical mixture of Nifedipine- Sepitrap 4000 are shown in figure No.3

2.3.5 Powder X-ray diffractometry (PXRD) Analysis:

The Powder X-ray diffraction technique has been extensively utilized along with DSC to study the interaction & to obtain the changes in the crystallanity of the physical mixtures of drug sepitrap prepared, the PXRD

study was carried out by using X-ray diffractometer (Miniflex 600 X-ray diffractometer, Rigaku corporation Japan) For this the samples of pure drug, physical mixtures of Nifedipine-sepitrap 80 & Nifedipine-sepitrap 4000 were irradiated with monochromatised CuKα radiation and analyzed between from 5° to 60° (2θ). The PXRD Diffractograms of Pure Nifedipine, Physical mixture of Nifedipine with sepitrap 80 & sepitrap 4000 are shown in figure no.4

2.3.6 Scanning Electron Microscopy (SEM) studies:

The surface morphology of pure Nifedipine & physical mixture of Nifedipine with Sepitrap 80 and sepitrap 4000 was observed by using a scanning electron microscope (VEG A3 TESCAN), under accelerating voltage of 15 keV. Samples were fixed on SEM stub with double-sided adhesive tape and then coated in a vacuum with thin gold layer before investigation. The SEM images of Nifedipine and its physical mixtures with sepitrap 80 & sepitrap 4000 are shown in figure 5

2.3.7 Photostability studies:

The Nifedipine is most photosensitive drug hence Photostability studies of pure Nifedipine & physical mixture of Nifedipine with sepitrap 4000 were done by exposing these samples to the fluorescent light using Photostability chamber (TP 00000906, Thermo lab). The Samples were assayed for their content of Nifedipine prior to exposure and at 4, 8, 12, 24, 36, and 60 h of continuous exposure using HPLC assay method. The chromatograms of pure Nifedipine and its physical mixture with sepitrap at different time interval are shown in fig no 6

2.3.8 Dissolution studies in SGF & SIF:

An accurately weighed amount of Nifedipine, physical mixture (equivalent to 20mg) of Nifedipine with sepitrap 80 & sepitrap 4000 in 1:1 & 1:2 proportion were weighed and added to the dissolution medium. The dissolution study was performed in simulated gastric fluid (pH 1.2) & simulated intestinal fluid (pH 6.8) .The dissolution study was carried out using USP apparatus II (Shimadzu UV spectrophotometer 1800) at 37±0.5 °C and 100 rpm paddle speed. The samples were withdrawn from dissolution media at specified time interval up to 120 min and the absorbance of the sample was recorded using UV spectrophotometer at 238 nm.[15]. The various dissolution profiles shown in figure no 7.

2.3.9 Stability Study:

Stability Study for Nifedipine –Sepitrap 4000 physical mixture (1:2 ratios) was carried out with the help of stability chamber (Remi SC-19 Plus) by storing 1gm of above physical mixture in an ambered colored screw capped glass bottles at accelerated and controlled temperatures 40°C and relative humidities (75%) for a period of 3 months. [32-34] Physical mixture was evaluated for physical appearance and in-vitro dissolution at the end of three months.

3. RESULT & DISCUSSION

3.1 Saturation solubility studies:

There was remarkable enhancement in the solubility of Nifedipine in presence of Sepitrap 80 and sepitrap 4000 compared to pure Nifedipine was observed in the saturation solubility studies. Pure Nifedipine exhibited a solubility of 8.30 ± 0.03 µg/mL in distilled water. The physical mixture of Nifedipine with sepitrap 80 in the proportion of 1:1 & 1:2 exhibited a solubility of 15.52 ± 0.04 and 21.90± 0.09 µg/mL respectively. The physical mixture of Nifedipine with sepitrap 4000 in the proportion of 1:1 & 1:2 exhibited a solubility of 22.43 ± 0.08 and 30.59 ± 0.02 µg/mL respectively. There was 263 % increase in the solubility in case of physical mixture of Nifedipine with sepitrap 80 in higher proportion that is 1:2 whereas 368 % increase in the solubility in case of physical mixture of Nifedipine with sepitrap 4000 in higher proportion that is 1:2. The enhancement in solubility of Nifedipine in presence of sepitrap 80 as well as sepitrap4000 clearly indicates the novel solubilizer in powder form that is Polysorbate 80 (sepitrap 80) & Polyoxyl 40 hydrogenated castor oil (sepitrap 4000) is promising for enhancement of solubility of poorly soluble drug. The solubility of Nifedipine and percent increase in solubility due to use of sepitrap 80 & sepitrap4000 are depicted in figure no.1

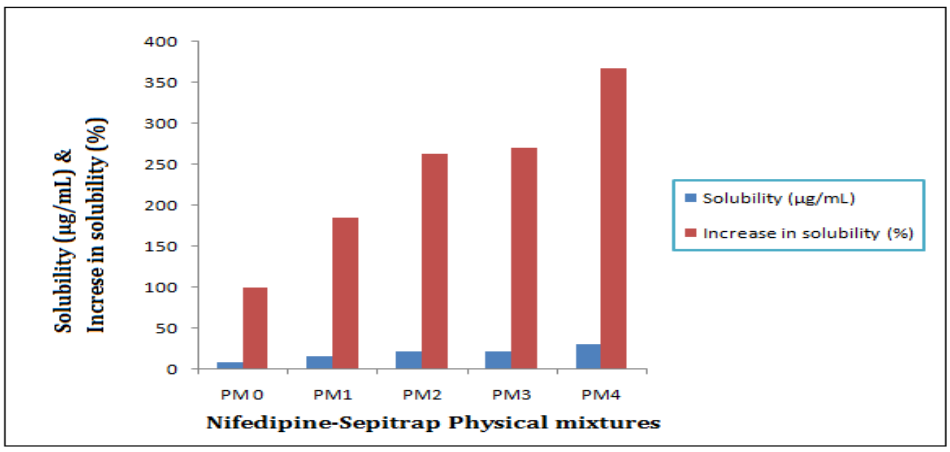

Figure 1: Saturation solubility of Nifedipine in distilled water with different proportions of sepitrap80 & sepitrap4000.

3.2 Fourier Transform Infrared spectrophotometer studies:

The FT-IT analysis has been carried out in order to study interaction between Nifedipine and its physical mixture with sepitrap80 & sepitrap 4000. Pure Nifedipine showed IR absorption bands at 1689 cm^{-1} for ester carbonyl stretching band, 1122 cm^{-1} and 1125 cm^{-1} for ether absorption bands of C_3 and C_5 respectively .The absorption band 1625, 1574 cm^{-1} were denoted for stretching vibration of C=C in the aromatic ring. The IR absorption peak at 1310 cm^{-1} and 1529.6 cm^{-1} denotes nitro group. The peak at 3333.10 cm^{-1} denotes N-H stretching. Pure IR spectra of sepitrap80 & sepitrap 4000 shows characteristics peaks and matches with standard reported peaks. The physical mixture of Nifedipine with sepitrap 80 & sepitrap4000 does not showed any new peaks and also retained principle IR peaks of pure Nifedipine which clearly indicates there is no any significant and unexpected interaction between Nifedipine and sepitrap. The overall results of FT-IR showed that sepitrap can be used as solubilizer for enhancement of solubility and dissolution rate as it found compatible with Nifedipine. FI-IR spectra of Pure Nifedipine, physical mixture of Nifedipine with sepitrap 80 & sepitrap4000 are shown in figure no.2

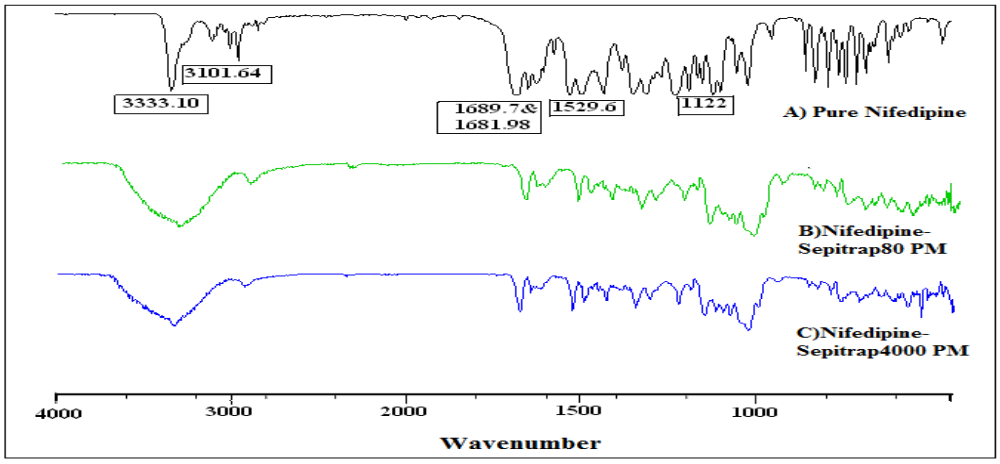

Figure 2: FT-IT Spectra of A] Pure Nifedipine, B] Physical Mixture of Nifedipine- Sepitrap 80 & C] Physical Mixture of Nifedipine –Sepitrap 400

3.3 Differential scanning calorimeter (DSC) Analysis:

Thermal analysis was also employed to evaluate drug crystallanity and to demonstrate any unexpected interaction between Nifedipine and sepitrap. A Sharp endothermic peak with an onset 172^{0}C and peak at 173.54^{0}C correspond to melting point of Nifedipine. The physical mixture of Nifedipine with sepitrap 80 showed broadening of peak with reducing peak intensity and actual peak observed at 166.96^{0}C. The physical mixture of Nifedipine with sepitrap4000 also showed broadening of peak with reducing peak intensity and actual peak observed at 169.12^{0}C. The peak broadening, reducing intensity and early onset as comparing to the pure Nifedipine indicates sepitrap 80 as well as sepitrap 4000 useful to reduction in drug's crystallanity and the dominance of its amorphous form which definitely affect in enhancement of solubility. The marked broadening and distinct reduction in intensity with shifting of drug endotherm was displayed physical mixture with sepitrap 80 and sepitrap 4000 demonstrate positive effect. The physical mixture sepitrap and drug only showed a reduction in onset of melting and peak value but there is no new peaks were found, this result revealed that there is no significant and unexpected interaction between drug and sepitrap 80 as well as sepitrap4000. The DSC thermogram of Pure Nifedipine, Sepitrap 80 & Sepitrap 4000 are shown in fig no. 3

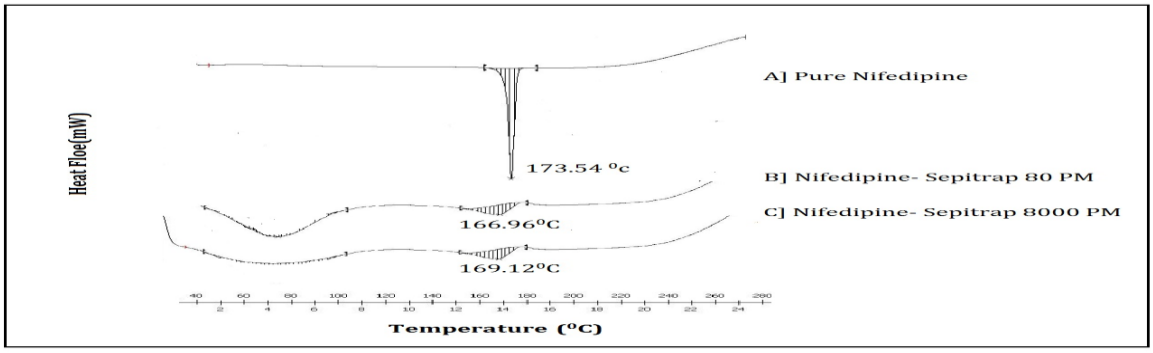

Figure 3: DSC Thermograms of A] Pure Nifedipine, B] Physical Mixture of Nifedipine- Sepitrap 80 & C] Physical Mixture of Nifedipine –Sepitrap 4000

3.4 Powder X-ray diffractometry (PXRD) Analysis:

Powder X-ray diffraction spectroscopy has been used to assess the degree of crystallanity of the given sample. When physical mixture of drug with sepitrap 80 & sepitrap 4000 are formed, the overall number of crystalline structures is reduced and the number of amorphous structures is increased. Thus, the final product sample shows fewer, less intense peaks. This shows that overall crystallanity of complexes is de-creased and due to a more amorphous nature, solubility is increased. The powder X-ray diffractograms of pure Nifedipine showed numerous distinctive peaks at 11.68, 11.70, 11.72, 11.74, 16.12 etc that indicated a high crystallanity. The physical mixture of Nifedipine with Sepitrap 80 & sepitrap 4000 distinctive peaks but reduction in peak intensity in terms of counts. No new peak was detected and hence there was no unfavorable interaction of the drug with sepitrap taking place. IR and DSC studies support the same data, which is confirmed by x-ray diffractometry. The PXRD Diffractograms of Pure Nifedipine, Physical mixture of Nifedipine with sepitrap 80 & sepitrap 4000 are shown in figure no.4

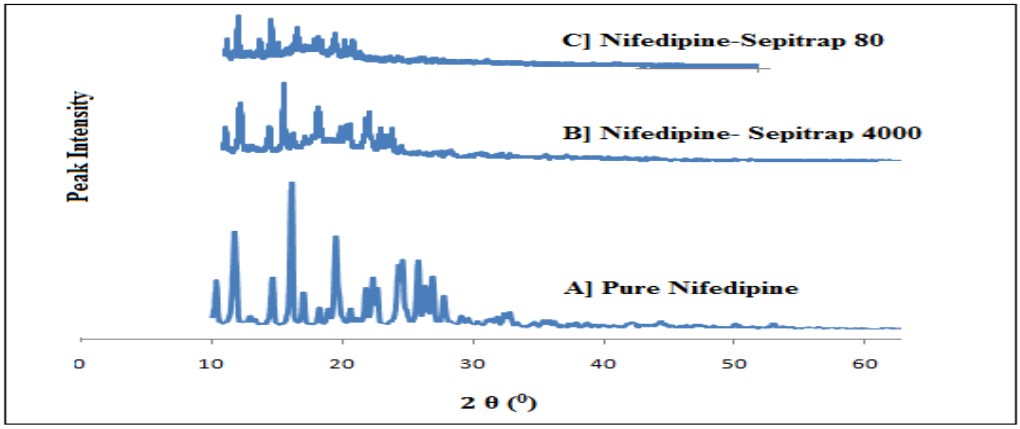

Figure 4: PXRD diffractograms for A] Pure Nifedipine, B] Physical Mixture of Nifedipine- Sepitrap 4000 & C] Physical Mixture of Nifedipine –Sepitrap 80

3.5 Scanning Electron Microscopy (SEM) studies:

The SEM study was done to check surface morphology of the drug particles and its relevant changes when mixed with solubilizer in powder for in various proportions as a physical mixture. Nifedipine particles were variable shaped with rough surface and exhibiting loose aggregates of irregular shape. The SEM of physical mixture of Nifedipine with sepitrap 80 not shows significant change in its surface morphology due to no use any solvent during the physical mixture preparation. The SEM study carried out on physical mixture of drug with sepitrap in two different ratios that is 1:1 & 1:2 to identify effect of concentration of solubilizer on surface morphology of Nifedipine. The SEM images of sepitrap4000 –Drug physical mixture shows slight changes in its surface structure due to hydrogenated castor oil in solid form. The slight change in structure also responsible for the enhancement of solubility when comes in contact with fluid medium. The SEM images of Nifedipine and its physical mixtures with sepitrap 80 & sepitrap 4000 are shown in figure 5

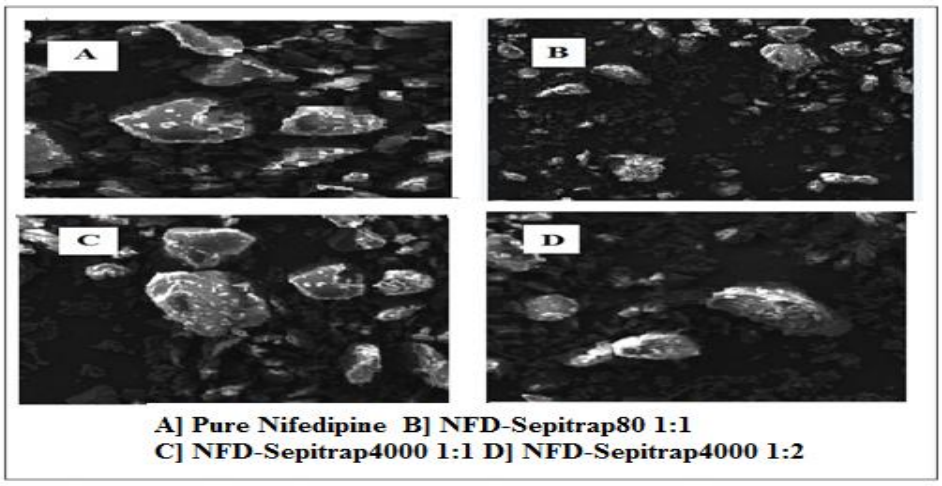

Figure5: SEM images of A] Pure Nifedipine, B] Physical Mixture of Nifedipine- Sepitrap 80 1:1 ratio & C] Physical Mixture of Nifedipine –Sepitrap 4000 1:1 ratio D] Physical Mixture of Nifedipine –Sepitrap 4000 1:2 ratio

3.6 Photostability studies:

The decomposition of Pure Nifedipine was found to be very marked upon exposure to fluorescent lamp or sunlight (which is the main source of light during manufacturing, storage and handling). The retention time for Nifedipine and its degradation product was found to be 14.02 ± 0.11 and 11.45 ± 0.24 respectively, thus it was clearly observed from the chromatograms that time required for 50% degradation of pure Nifedipine & Physical mixture with sepitrap was found to be around 8 & 12 h respectively. Time required for complete degradation of pure Nifedipine & Physical mixture with sepitrap around 24 h and more than 36 h respectively. This study indicates that the rate of photo degradation is very slow in Physical mixture with sepitrap as compared to pure Nifedipine .The physical mixture containing sepitrap 4000 may protects the Nifedipine from photodegradation as the photodegradation is surface phenomenon and sepitrap protect Nifedipine from direct exposure of light. The chromatograms of pure Nifedipine and its physical mixture with sepitrap at different time interval are shown in fig no 6

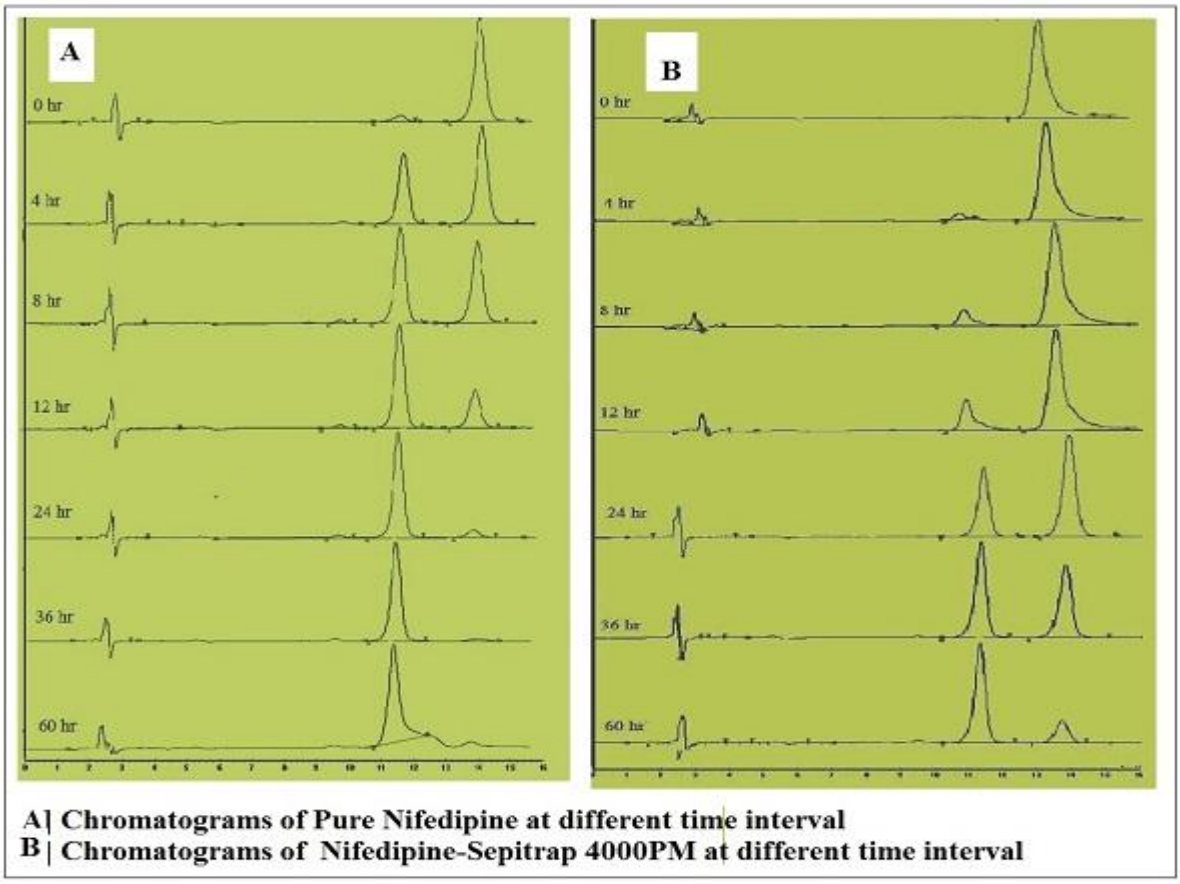

Figure 6: chromatograms of A] Pure Nifedipine at different time interval B] Nifedipine-Sepitrap 4000 physical mixture at different time interval

3.7 In-Vitro Dissolution studies in SGF & SIF:

The dissolution study was carried out in simulated gastric fluid as well as simulated intestinal fluid. The pure Nifedipine shows drug dissolution of 16. 24 & 18.21 % in 30 min in SGF & SIF respectively, Physical mixture of Nifedipine with sepitrap 80 in 1: 2 proportion shows 56.78 & 63.22% drug dissolution in 30 min while Physical mixture of Nifedipine with sepitrap 4000 in 1: 2 proportion shows 70.28 & 71.54 % drug dissolution in SGF & SIF respectively. The dissolution of Nifedipine was significantly enhanced by use of novel solubilizer sepitrap 80 as well as sepitrap 4000 in 1:2 proportions. The enhancement in Nifedipine dissolution was explained to be mainly due to the increase in both wettability and solubility. The solubility of pure Nifedipine increased due to localized solubilization in presence of novel solubilizer sepitrap 80 &sepitrap 4000 resulted in overall increase in dissolution rate. The Physical mixture containing Nifedipine –sepitrap 80 in 1:2 proportion shows similar dissolution profile compare to physical mixture containing Nifedipine –sepitrap 4000 in 1:1 proportion indicate that sepitrap 4000 is more potential and effective solubilizer as compare to sepitrap 80 in exactly half quantity to that of sepitrap80. The dissolution profile of all physical mixture in simulated gastric fluid & simulated intestinal fluid not shows any significant difference indicating novel solubilizer sepitrap 80 as well as sepitrap 4000 is effective as solubilization agent in various pH condition of GI tract. The dissolution profiles of various physical mixtures in simulated gastric fluid and simulated intestinal fluid are shown in figure No.7

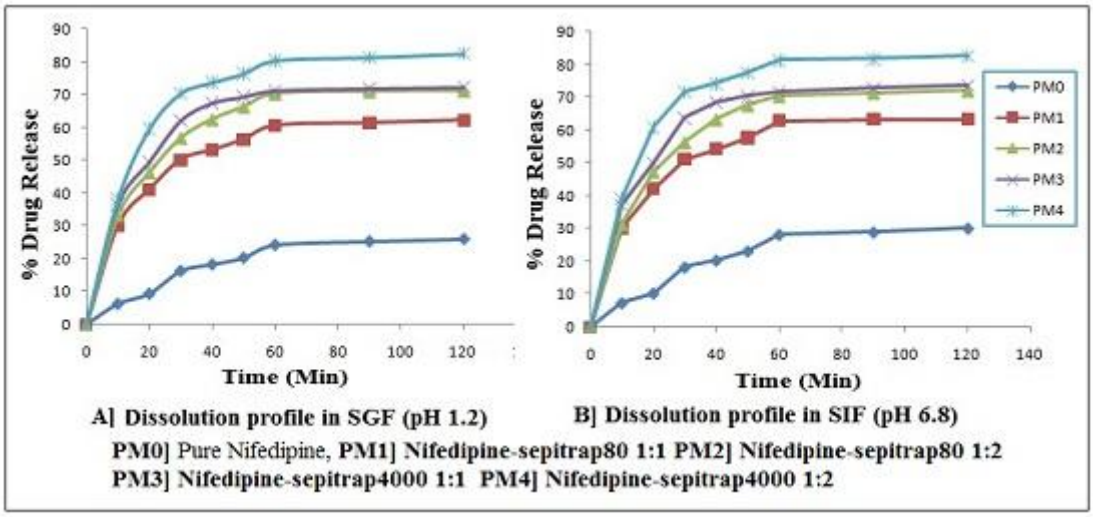

Figure 7: Dissolution profile in A] simulated gastric fluid pH 1.2 and B] Simulated intestinal fluid pH 6.8

3.9 Stability studies:

There was no significant change in the physical appearance and percent drug dissolution in the physical mixture of Nifedipine-sepitrap4000 in 1:2 ratio. A stability results clearly indicate that the physical mixture was sufficiently stable under accelerated and controlled conditions. The no change in physical appearance clearly indicates that sepitrap 4000 was stable under accelerated temperature condition and hence overall physical mixture containing drug remains stable.

4. CONCLUSION

The use of novel solubilizer sepitrap 80 & sepitrap4000 in the form of simple physical mixture was proven to successful approach for solubility and dissolution rate enhancement of poorly soluble BCS class II drug Nifedipine. In-vivo pharmacokinetic study in albino rats clearly indicates that sepitrap 4000 in 1:2 proportions is most useful in the form simple physical mixture for enhancement of absorption of Nifedipine as compare to the drug alone. Nifedipine –sepitrap 4000 physical mixture can be used for further development in any suitable drug delivery technique where poor solubility of active ingredient becomes rate limiting step.

5. Acknowledgement

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